

## COMMENTARY

# Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia

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In late December 2019, a new infectious disease emerged in the city of Wuhan in Hubei Province, China. A novel betacoronavirus, 2019-nCoV, capable of human-to-human transmission, has been identified as the causative pathogen in this disease.<sup>1,2</sup> In recent years, two other betacoronavirus epidemics have been identified as the cause of acute severe respiratory disease: in 2003, Severe Acute Respiratory Syndrome (SARS) and in 2012, Middle East Respiratory Syndrome (MERS). In all of these diseases, the initial source of the virus appears to be other animal species (civets for SARS and dromedary camels for MERS), and although the immediate animal source for the 2019-nCoV agent remains to be determined, bats are likely the common source for all of these RNA betacoronaviruses.<sup>2,3</sup>

At the time of writing, the 2019-nCoV epidemic is still advancing and its ultimate toll is far from clear. Latest numbers estimate >78 000 people infected worldwide, with >76 000 cases and 2345 deaths in China alone. 2019-nCoV cases have now been confirmed in 28 other countries.

In this issue of the journal, Tang and colleagues from the Tongji Medical College in Wuhan (the initial source of the 2019-nCoV epidemic) describe their experience with the association of 2019-nCoV pneumonia and disseminated intravascular coagulation (DIC) over the first 6 weeks of the epidemic. Their findings highlight that evidence of DIC is a strong predictor of mortality in patients developing pneumonia with this virus.

The spectrum of clinical manifestations of 2019-nCoV infection includes fever, myalgia, cough and dyspnea, and less frequently headache, diarrhea, nausea and vomiting.<sup>4</sup> The prevalence of an asymptomatic form of this disease is yet to be determined. In those patients demonstrating clinical symptoms, progression to pneumonia appears frequent, with imaging evidence of parenchymal disease, acute respiratory

distress occurring in 30% of patients, 30% requiring intensive care unit admission, and 10% to 15% of patients dying from their disease.<sup>4</sup> High plasma levels of proinflammatory cytokines (interleukin-2, interleukin-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A, and tumor necrosis factor- $\alpha$ ) have been observed in 2019-nCoV patients admitted to intensive care units, suggesting that a cytokine storm effect may be developing in these individuals with severe disease.<sup>4</sup>

In the 2003 SARS epidemic that originated in Guangdong Province, China, >8000 cases were documented, with 744 deaths. SARS-related mortality varied significantly from 0% to 17%, depending on geographical location.<sup>5</sup> The hematologic complications of SARS included 63% of patients demonstrating isolated transient elevations of the activated partial thromboplastin time in the first 2 weeks of infection, but most patients had normal prothrombin times and no elevation of D-dimers. A total of 2.5% of SARS patients showed evidence of DIC, and this was frequently associated with mortality.<sup>6</sup>

In their timely report, Tang et al describe the outcome of 183 patients admitted to the Tongji Hospital in Wuhan with RNA detection confirmed 2019-nCoV pneumonia during the period January 1 through February 3, 2020. The clinical outcomes are reported up to February 13, 2020. The mean age of patients was 54 years, and 41% had comorbid chronic diseases (cardiovascular, respiratory, cancer, liver, and kidney). All patients received treatment with supportive care and antiviral agents. At the time of reporting, 42.6% of patients had been discharged from the hospital, 45.9% remained as inpatients, and the overall mortality was 11.5%. Patients were tested for prothrombin time, activated partial thromboplastin time, antithrombin, fibrinogen, D-dimer, and fibrin degradation products every 3 days for the first 2 weeks of hospital stay. Applying the validated International Society on Thrombosis and Haemostasis DIC score,<sup>7</sup> 71.4% of nonsurvivors and 0.6% of survivors showed evidence of overt DIC, with the median time to DIC detection being

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4 days. The authors conclude, based on these preliminary results from a single center, that DIC is a frequent occurrence in worsening 2019-nCoV pneumonia and is often associated with mortality. Evidence of DIC, especially elevated D-dimer levels, may be used in therapy considerations.

This account of the involvement of the hemostatic system in severe 2019-nCoV pneumonia will not come as a major surprise to the hemostasis community, for which the involvement of sepsis as an initiator of DIC is very well documented.<sup>8</sup> Nevertheless, whether this particular virus is more prone to DIC development will need to be followed closely as this epidemic evolves.

The pathophysiology of DIC is complex and multifactorial, involving an interplay between cellular and plasmatic elements of the hemostatic system and components of the innate immune response to the infecting pathogen.<sup>9</sup> Activation of the vascular endothelium, platelets, and leukocytes results in dysregulated thrombin generation that occurs both systemically and locally in the lungs of patients with severe pneumonia, resulting in the deposition of fibrin with subsequent tissue damage and microangiopathic pathology. There is evolving evidence that a combination of activation events initiated by exposure of the endothelium, platelets, and leukocytes to pathogen- and damage-associated molecular patterns are the primary instigators of this pathophysiology.<sup>10</sup> The effects of dysregulated thrombin generation are further exacerbated by an inhibition of fibrinolysis and the impairment of natural anticoagulant mechanisms. To date, treatment of DIC has been focused on strategies to target the primary associated pathology<sup>11</sup>; this, of course, is limited in the case of 2019-nCoV infection, until more is learnt about effective antiviral agents for this new pathogen. Otherwise, supportive care to maintain critical organ function is required. Trials of natural anticoagulant infusions have met with variable outcomes,<sup>12</sup> although recent experience with a soluble thrombomodulin product appears promising.<sup>13</sup>

As the 2019-nCoV epidemic progresses, we will learn more about the propensity of this agent to engage both innate immune and hemostatic systems, two critical emergency response pathways that maintain homeostasis under controlled circumstances, but that produce severe pathologies of their own when present under

dysregulated conditions. The observations of Tang and colleagues provide early evidence that enhanced vigilance is required to identify the emergence of DIC in 2019-nCoV pneumonia patients.

## CONFLICTS OF INTEREST

The author declares that they have no conflicts of interest.

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